Stelara

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0108	Extension of indication to include treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy or have medical contraindications to such therapies for	27/02/2025	31/03/2025	SmPC and PL	Please refer to Scientific Discussion: Stelara EMEA/H/C/000958/II/0108

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	STELARA, based on final results from study CNTO1275CRD3004. This is a Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open label Intravenous Induction Treatment Followed by Randomised Double blind Subcutaneous Ustekinumab Maintenance in Paediatric Participants with Moderately to Severely Active Crohn's Disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 29.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0107	Update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information based on results from study CNTO1275CRD1003. This is a phase 1, open-label, drug interaction study to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in participants with active Crohn's disease or ulcerative colitis. In addition, the MAH took the opportunity to update sections 4.8 and 5.1 to include patient exposure numbers based on results from study CNTO1275UCO3001. This is a phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis.	19/12/2024	31/03/2025	SmPC and PL	SmPC new text Regulation of CYP450 enzymes The effects of IL 12 or IL 23 on the regulation of CYP450 enzymes were evaluated in an in vitro study using human hepatocytes, which showed that IL 12 and/or IL 23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5). A Phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19

	During the procedure the MAH has also taken the opportunity to update the PI based on the QRD template, which includes a warning on the polysorbate threshold. The requested variation proposed amendments to the Summary of Product Characteristics & Patient Information Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5). For more information, please refer to the Summary of Product Characteristics.
PSUSA/3085/ 202312	Periodic Safety Update EU Single assessment - ustekinumab	25/07/2024	25/09/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3085/202312.
II/0104	Submission of the final report from study RRA-20745 listed as a category 3 study in the RMP. This is an observational post-authorization safety study (PASS) to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease. Consequently, the SmPC section 4.4 was amended. The RMP version 30.1 has also been updated. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/09/2024	31/03/2025	SmPC	The variation updated the warning on malignancies in the SmPC section 4.4 by broadening the scope of monitoring for the appearance of all skin cancers, including melanoma. For more information, please refer to the Summary of Product Characteristics.
IB/0106/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a	31/07/2024	n/a		

	biological/immunological medicinal product B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product				
II/0100	Update of section 4.6 of the SmPC in order to update information on pregnancy based on the final synoptic report from study CNTO1275PSO4037 (OTIS); this is a pregnancy exposure registry for Stelara. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct 3 editorial discrepancies in the SmPC sections 4.8 and 6.6 and package leaflet section 5. The consolidated RMP version 28.1 has also been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/06/2024	25/09/2024	SmPC and PL	Data from a moderate number of prospectively collected pregnancies following exposure to STELARA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of Stelara in pregnancy. For more information, please refer to the Summary of Product Characteristics.
II/0101/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2024	n/a		
IB/0103	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/09/2023	n/a		

PSUSA/3085/ 202212	Periodic Safety Update EU Single assessment - ustekinumab	31/08/2023	n/a		PRAC Recommendation - maintenance
IA/0102/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	25/07/2023	n/a		
IB/0099	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/07/2023	n/a		
II/0098/G	This was an application for a group of variations. Type II (B.IV.1.c) - to add a new Pre-filled Pen (PFP) presentation, for Stelara 45 mg solution for injection (EU/1/08/494/006) Type IAIN (B.II.e.5.a) - To add a new PFP presentation for Stelara 90 mg solution for injection (EU/1/08/494/007) The RMP has been updated. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is	25/05/2023	15/11/2023	SmPC, Labelling and PL	Introduction of new pre-filled pen presentations, for Stelara 45 mg and 90 mg solution for injection, supported by a bioequivalence, user testing and Human Factors Studies. A new SmPC, PIL and Instructions for Use have been provided for the new prefilled pen presentations (EU/1/08/494/006-007). The SmPCs for the concentrate for solution for infusion, solution for injection in pre-filled syringe and vials have been updated in section 4.2 and 5.1 and 5.2 to reference the new formulation and to indicate that the bioavailability of ustekinumab following administration by syringe or pre-filled pen is comparable. For more information, please refer to the Summary of Product Characteristics. The PL for the new pre-filled pen is in line with the PL for other formulations.

	an integrated part of the primary packaging				
II/0096	Update of section 5.1 of the SmPC in order to update information with the 4-year clinical data in patients with ulcerative colitis based on the final report from study CNTO1275UCO3001 listed as a category 3 study in the RMP; this is a phase 3, randomised, double blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. The RMP version 24.1 has also been updated. In addition, the MAH took the opportunity to introduce a correction to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2023	15/11/2023	SmPC	In UNIFI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 400 patients who entered on and were treated with ustekinumab every 12 or 8 weeks in the study extension, symptomatic remission was generally maintained through week 200 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. Among patients who received 4 years of ustekinumab treatment and were assessed using the full Mayo score at maintenance week 200, 74.2% (69/93) and 68.3% (41/60) maintained mucosal healing and clinical remission, respectively. For more information, please refer to the Summary of Product Characteristics.
II/0095	Submission of the final report from study PSOLAR (C0168Z03) listed as a category 3 study in the RMP. This is a Multicenter, Open Registry of Patients with Psoriasis Who Are Candidates for Systemic Therapy Including Biologics: PSOLAR. As a consequence, section 4.4 has been updated to amend the warning on the risk of infections and malignancy, and to include a warning on the risk of major adverse cardiovascular events (MACE). The Package leaflet is updated accordingly. The RMP version 23.2 has also been updated. C.I.13 - Other variations not specifically covered	16/03/2023	15/11/2023	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

	elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/3085/ 202112	Periodic Safety Update EU Single assessment - ustekinumab	15/09/2022	09/11/2022	SmPC and PL	Please refer to EPAR: scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0091	Update of the SmPC section 4.4, 4.5 and 4.6 with recommendation not to administer live vaccines to infants for six months following birth unless ustekinumab infant serum levels are undetectable or there is clear clinical benefit for the individual infant. The update follows assessment of the final safety registry report of CNTO1275PSO4007 "Pregnancy Research Initiative: Exposure to ustekinumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers." Consequently, the PL and the RMP version 22.1 have also been updated. Additionally, minor editorial changes and updates to the list of representatives were introduced. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	27/10/2022	15/11/2023	SmPC and PL	SmPC new text Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth. Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for 6 months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable. For more information, please refer to the Summary of Product Characteristics.
II/0094/G	This was an application for a group of variations. B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	01/09/2022	n/a		

IA/0093/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	21/03/2022	n/a		
PSUSA/3085/ 202012	Periodic Safety Update EU Single assessment - ustekinumab	16/09/2021	12/11/2021	SmPC and PL	Please refer to Stelara EMEA/H/C/PSUSA/00003085/202012 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0089	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/05/2021	n/a		
IB/0088	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	19/04/2021	n/a		
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/04/2021	12/11/2021	PL	
II/0081/G	This was an application for a group of variations. Update of section 4.2 of Stelara SmPC solution for injection presentations in order to change posology recommendations for patients with ulcerative colitis,	28/01/2021	09/03/2021	SmPC	Section 4.2 of Stelara SmPC solution for injection is updated to indicate that if therapy is interrupted in patients with ulcerative colitis, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective. Section 5.1 of Stelara SmPC is updated with efficacy

	and 5.1 of Stelara SmPC to update efficacy information based on 2-year results from study 3001 listed as a category 3 study in the RMP; this is a Phase 3, randomized, double blind, placebo controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. Update of section 5.1 of the SmPC in order to update efficacy information based on 5-year results from study 3003 listed as a category 3 study in the RMP; this is a Phase 3, randomized, double blind, placebo controlled, parallel-group, multicenter trial to evaluate the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease. The RMP version 18.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				information based on 2-year results of the extension from UNIFI study in patients with ulcerative colitis: among the 588 patients who entered and were treated in the study extension, symptomatic remission was generally maintained through week 92 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. No new safety concerns were identified in this study extension with up to 2 years of treatment in patients with ulcerative colitis. Section 5.1 of Stelara SmPC is updated with 5-year results of the extension from IM-UNITI study in patients with Crohn's disease: among the 718 patients who entered and were treated in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies. No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.
IB/0086	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/03/2021	n/a		
IA/0085	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	11/02/2021	n/a		

II/0082	To submit the final safety registry report of CNTO1275PSO4005 "Nordic Database Initiative for Exposure to Ustekinumab: a Review and Analysis of Adverse Events from the Swedish and Danish National Registry Systems" listed as a category 3 in the RMP. An updated RMP version (18.2) has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/02/2021	n/a		The MAH submitted the final study report of the category 3 Nordic database initiative, a prospective cohort study base on secondary data collection from the Danish and Swedish national registers. The study conducted in adult patients with psoriasis with or without psoriatic arthritis. Overall, the study results appear consistent with the known safety profile of ustekinumab. No new safety signal was identified. Based on the result of this study no update to the product information was required. In RMP version 19.1 the information regarding category 3 Nordic database initiative has been updated to reflect that this study has been completed. All corresponding sections of the RMP have been updated accordingly.
IB/0084	C.I.7.b - Deletion of - a strength	07/12/2020	11/01/2021	SmPC, Labelling and PL	
II/0083	Update of section 4.8 of the SmPC in order to add hypersensitivity vasculitis to the list of adverse drug reactions (ADRs) with frequency rare based on cumulative review from the literature and post-marketing reporting; the Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/11/2020	11/01/2021	SmPC and PL	Following a cumulative review carried out by the MAH, several cases of leukocytoclastic (hypersensitivity) vasculitis were identified post marketing setting and, in the literature, including cases describing a positive de-challenge and positive re-challenge. Based on biological plausibility, hypersensitivity vasculitis is added as an adverse drug reaction in section 4.8 of the SmPC with frequency rare. The Package leaflet has been updated accordingly.

II/0080/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	09/07/2020	n/a		
PSUSA/3085/ 201912	Periodic Safety Update EU Single assessment - ustekinumab	09/07/2020	n/a		PRAC Recommendation - maintenance
IB/0079	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/06/2020	n/a		
IB/0076	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/04/2020	n/a		
IB/0077	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/03/2020	n/a		
II/0073	Extension of indication to include the treatment of children aged ≥6 to <12 years with moderate to severe psoriasis for Stelara solution for injection; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and	12/12/2019	20/01/2020	SmPC and PL	Please refer to the Scientific Discussion Stelara EMEA/H/C/000958/II/0073

	6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Section 4.8 for Stelara concentrate for solution for infusion is updated accordingly. Minor editorial changes are made to Section 4.5 for both formulations. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 16.1 has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0075	To change the storage conditions of the biological medicinal product Stelara, prefilled syringe (PFS) to allow drug product storage for a maximum single period of up to 30 days at room temperature up to 30 °C, after storage at 2 to 8 °C, in the original carton protected from light and not to exceed the current established shelf life of Stelara PFS. Furthermore, the PI is being brought in line with the latest QRD template version 10.1. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	16/01/2020	11/01/2021	SmPC, Annex II, Labelling and PL	Sections 6.3 and 6.4 of the SmPC are updated to reflect the optional storage condition at room temperature for Stelara PFS. The PL and labelling have been updated accordingly.
IA/0074	A.7 - Administrative change - Deletion of manufacturing sites	20/09/2019	n/a		

PSUSA/3085/ 201812	Periodic Safety Update EU Single assessment - ustekinumab	25/07/2019	16/09/2019	SmPC and PL	Please refer to Stelara EMEA/H/C/PSUSA/00003085/201812 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0071	Extension of Indication for Stelara to include treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. As a consequence, the SmPC, Package Leaflet and RMP have been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2019	03/09/2019	SmPC and PL	Please refer to Scientific Discussion: Stelara EMEA/H/C/000958/II/0071
II/0070/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study	13/12/2018	n/a		
II/0066	Update of section 4.8 of the SmPC to add allergic alveolitis and eosinophilic pneumonia as rare adverse	29/11/2018	03/09/2019	SmPC and PL	Section 4.4 of the SmPC has been updated to reflect that cases of allergic alveolitis and eosinophilic pneumonia have

	reaction. A warning in section 4.4 of the SmPC has also been added to reflect that cases of allergic alveolitis and eosinophilic pneumonia have been reported during post-approval use of ustekinumab. The PL is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, is recommended to discontinue ustekinumab and institute appropriate treatment. Section 4.8 of the SmPC has also been updated to add allergic alveolitis and eosinophilic pneumonia as rare adverse reaction. The PL has been updated accordingly.
IB/0068	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/10/2018	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	03/09/2019	PL	
PSUSA/3085/ 201712	Periodic Safety Update EU Single assessment - ustekinumab	26/07/2018	17/09/2018	Annex II	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3085/201712.
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	20/08/2018	03/09/2019	Annex II	
II/0063	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/07/2018	17/09/2018	SmPC and PL	
IAIN/0065	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	31/05/2018	n/a		

	site				
II/0062/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	15/03/2018	n/a		
IB/0061	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	21/02/2018	17/09/2018	SmPC and PL	
II/0060	Update of sections 4.8 and 5.1 of the SmPC to update the efficacy data following completion of extension of study IM-UNITI - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohns Disease. In addition, the marketing authorisation holder took the opportunity to introduce editorial changes in the SmPC and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2018	17/09/2018	SmPC and PL	The SmPC section 4.8 and 5.1 has been updated as follows: - 4.8 - No new safety concerns were identified with up to 2 years of treatment in patients with Crohn’s Disease. - 5.1 - In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92 for both patients who failed TNF-therapies and those who failed conventional therapies. Improvement in health related quality of life was generally maintained during the extension through week 92.

IB/0059/G	This was an application for a group of variations. B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	09/12/2017	30/01/2018	SmPC and PL	
II/0058	Update of section 4.8 of the SmPC in order to include Lower Respiratory Tract Infection as an Adverse Drug Reaction based on a comprehensive evaluation of safety information from the STELARA clinical studies database and post-marketing database, as well as available literature. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	30/01/2018	SmPC and PL	Update of section 4.8 of the SmPC in order to include Lower Respiratory Tract Infection as an Adverse Drug Reaction based on a evaluation of safety information from the ustekinumab clinical studies database and post-marketing database, as well as available literature. The Package Leaflet has been updated accordingly to prompt patients or carers to inform the doctor straight away if signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications
PSUSA/3085/ 201612	Periodic Safety Update EU Single assessment - ustekinumab	06/07/2017	n/a		PRAC Recommendation - maintenance
IA/0057	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	03/05/2017	n/a		
IA/0056/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	30/03/2017	n/a		

	specification limits B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0054	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	30/03/2017	30/01/2018	SmPC	
IA/0053/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	24/02/2017	30/01/2018	Annex II	
IA/0052	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/02/2017	n/a		
II/0051/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.f - Change in the batch size (including batch	24/11/2016	n/a		

	size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
X/0049/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/09/2016	11/11/2016	SmPC, Labelling and PL	
PSUSA/3085/ 201512	Periodic Safety Update EU Single assessment - ustekinumab	07/07/2016	n/a		PRAC Recommendation - maintenance
II/0048	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	07/07/2016	n/a		
IA/0047/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	28/07/2015	15/07/2016	Annex II	

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
PSUSA/3085/ 201412	Periodic Safety Update EU Single assessment - ustekinumab	09/07/2015	n/a		PRAC Recommendation - maintenance
II/0042	Extension of Indication to add treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. As a consequence SmPC sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.1 and 6.6 have been updated and the Package Leaflet has been updated accordingly. A revised RMP version 12.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/05/2015	22/06/2015	SmPC and PL	Please refer to the Scientific Discussion 'Stelara-H-C-958-II-42'.
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
II/0044/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a	26/02/2015	n/a		

	biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
II/0041	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2014	21/11/2014	SmPC and PL	
IA/0043/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	30/10/2014	22/06/2015	Annex II	
PSUV/0040	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance

II/0036	Update to section 5.1 of the SmPC with data showing that ustekinumab reduces the rate of progression of peripheral joint damage. The package leaflet has been updated accordingly. Section 4.8 of the SmPC has been updated with data from the phase 3 studies of ustekinumab in psoriatic arthritis (PsA). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	21/11/2014	SmPC and PL	Please refer to the scientific discussion Stelara EMEA/H/C/000958/II/0036 for further information.
II/0037	Extension of indication to include the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). Section 1 of the Package Leaflet has been updated accordingly C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/01/2014	21/02/2014	SmPC and PL	Please refer to the scientific discussion Stelara EMEA/H/C/000958/II/0037 for further information.
IB/0039/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	15/01/2014	n/a		

N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2013	21/02/2014	PL	
R/0034	Renewal of the marketing authorisation.	25/07/2013	19/09/2013	SmPC, Annex II and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Stelara continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Stelara continues to be favourable.
II/0029	Extension of indication to include the treatment of psoriatic arthritis. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package leaflet has been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2013	19/09/2013	SmPC and PL	Please refer to the scientific discussion Stelara EMEA/H/C/000958/II/0029 for further information.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0033	Addition of pustular psoriasis as an adverse drug reaction in section 4.8 of the SmPC and in section 4 of the package leaflet, based on safety information from Stelara clinical trial and post-marketing data. The MAH took the opportunity to update the list of local representatives in the package leaflet. C.I.4 - Variations related to significant modifications	25/07/2013	19/09/2013	SmPC and PL	Following a cumulative review of ustekinumab in association with pustular psoriasis including assessment of cases derived from clinical studies and post-marketing experience, the MAH identified 15 cases of rash pustular and 6 cases of pustular psoriasis in a pool of psoriasis phase 2 and 3 studies. In terms of post-marketing experience the MAH identified no serious cases of pustular psoriasis with ustekinumab in

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the PSOLAR database and 2 non-serious events of possible pustular psoriasis which are not considered significant evidence for this variation. A total of 61 cases of pustular psoriasis/rash pustular were identified in the SCEPTRE database. Forty (40) cases were assessed as de novo pustular psoriasis, 10 cases concerned patients with a known history of pustular psoriasis, 8 cases reported the indication of ustekinumab as some type of pustular psoriasis and the remaining 3 cases reported patients who had pustular disease when ustekinumab was initiated but did not clearly state pustular psoriasis as the indication. Therefore, "pustular psoriasis" is added as an adverse drug reaction in section 4.8 of the SmPC with category uncommon and in section 4 of the package leaflet.
II/0030/G	This was an application for a group of variations. To add a post approval change management protocols to introduce new manufacturing sites for the drug substance B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	25/04/2013	n/a		
IB/0031	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal	22/02/2013	19/09/2013	SmPC	

	product in accordance with an approved stability protocol				
IA/0032	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	01/02/2013	n/a		
II/0028	Update of section 4.4 and 4.8 of the SmPC regarding the need to monitor the appearance of non-melanoma skin cancer in all patients. Update of section 4.4 and 5.1 of the SmPC regarding the lack of suppression of humoral immune response to pneumococcal polysaccharide or tetanus vaccines after long term treatment with Stelara. Exposure numbers in section 4.8 have also been updated in accordance with the 5-year safety update for studies C0743T08 and C0743T09. Section 4.9 of the SmPC has also been amended with the updated single IV dose of Stelara at which no direct toxic effect is observed. Section 2 of the package leaflet has been updated with a wording regarding the need to tell the doctor before taking Stelara in case the patient has ever had an allergic reaction to Stelara (or if the patient is not sure about it) or if the patient has any new or changing lesions within psoriasis areas or on normal skin. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	17/01/2013	19/09/2013	SmPC and PL	Results with up to 5 years of treatment with ustekinumab in subjects with moderate to severe psoriasis and updated information on potential overdosing of ustekinumab have provided additional information on safety, efficacy, pharmacokinetic, and immunogenicity. The overall safety database has increased and no major changes in the known safety profile for Stelara have emerged. No cumulative safety signals have been seen over 5 years follow-up and the rates of AEs and SAEs are consistent with year 3 and year 4 data. With the larger safety data base, six (6) cases of melanoma (one with invasive melanoma) were identified. There is no evidence of a dose-response with ustekinumab for the development of melanoma. However, the event of melanoma has been added in section 4.8 of the SmPC and will continue to be monitored. Information from the literature identified 2 patients older than 60 years of age, who developed multiple cutaneous squamous cell carcinomas (SCCs) after each receiving 2 doses of ustekinumab. Therefore, a warning regarding the need to monitor all patients for the appearance of non-melanoma skin cancer has been added in the SmPC. New data has been provided on vaccination responses to tetanus and pneumococcal vaccination. The results show no

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				impairment of antibody responses to these vaccinations in subjects who have received Stelara for at least 3.5 years. The above information has been included in sections 4.4 and 5.1 of the SmPC and is considered by the CHMP to be in line with the 5-year clinical trial update and the results from the vaccine substudy. In addition the maximum dose given without safety signals is now 6mg/kg since intravenous dosing up to 6 mg/kg was evaluated in the C0743T26 Phase 2b trial of ustekinumab in Crohn's disease. Section 4.9 of the SmPC has been updated accordingly. Moreover, the exposure numbers in the SmPC have been updated in line with the 5-year clinical update for studies C0743T08 and C0743T09. Information regarding the presence of neutralizing antibodies has been included in section 4.8 of the SmPC as approximately 75% of ADA positive subjects had Nab. The benefit/risk balance for Stelara in the treatment of psoriasis is positive and a further key benefit has been provided in the data for this variation; namely the demonstration that after at least 3.5 years treatment with Stelara vaccination responses to tetanus and to pneumococcus are not impaired compared with subjects who have not received Stelara.
IB/0027	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	24/09/2012	n/a		
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
IB/0025	B.II.f.1.b.5 - Stability of FP - Extension of the shelf	05/06/2012	29/10/2012	SmPC	

	life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol				
IB/0024	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	03/04/2012	n/a		
II/0022/G	This was an application for a group of variations. Addition of an alternative testing site for Active substance. Introduction of additional assays for active substance testing. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	15/03/2012	15/03/2012		
II/0021	Update of section 4.8 of the SmPC to include facial palsy and arthralgia as adverse drug reactions, and update of the PL accordingly, further to post-marketing and clinical trials data from PSUR 4. Additionally, the product information was updated	19/01/2012	21/02/2012	SmPC, Annex II, Labelling and PL	Both facial palsy and arthralgia have been observed in the post-marketing setting as well as in clinical trials. In accordance with the European Commission Guideline on Summary of Product Characteristics (September 2009), the MAH has calculated the frequency of these ADRs based on

	according to the latest QRD template. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				clinical trial data. In order to be consistent with the rates already described in the ADR table of the SmPC, the incidence rate of facial palsy is based on 2 cases in 2,266 (0.09%) subjects exposed to Stelara in psoriasis clinical studies and the assigned frequency category is "rare". Similarly, the incidence rate of arthralgia is based on 159 cases in 2,266 (7.02%) subjects exposed to Stelara in psoriasis clinical studies and the assigned frequency category is "common".
II/0018	Update of sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) with longer-term efficacy and safety information of continuous ustekinumab administration based on up to 4 year clinical trial data. The Package Leaflet (PL) is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 7.3.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	13/01/2012	SmPC and PL	The currently approved product information for Stelara provides efficacy data on the maintenance of clinical response with q12 week dosing up to 52 weeks and safety data reflecting exposure to ustekinumab in 2266 psoriasis subjects (2251 patient-years of exposure), including 1970 exposed for at least 6 months, 1285 exposed for at least one year, and 373 exposed for at least 18 months. With this variation, the product information of Stelara is updated with information on the long-term maintenance of efficacy and safety information of continuous ustekinumab administration based on up to 4 year clinical trial data.
IB/0023	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	16/12/2011	n/a		
II/0017/G	This was an application for a group of variations. Additional site for the manufacture of the finished	17/11/2011	17/11/2011		

	product. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IA/0016/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	29/07/2011	n/a	Annex II	
II/0015/G	This was an application for a group of variations. This was an application for a group of variations: Update of sections 4.5 and 5.2 of the SmPC regarding the potential for interleukin IL-12 and IL-	23/06/2011	26/07/2011	SmPC	The effects of IL 12 or IL 23 on the regulation of CYP450 enzymes were evaluated in an in vitro study using human hepatocytes, which showed that IL 12 and/or IL 23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). This

	23 (separate and in combination) to alter the functional activity and mRNA expression of various CYP450 isoforms. Update of section 5.2 of the SmPC regarding pharmacokinetic findings in Asian patients of the C0743T25 study, as requested by the CHMP. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				information is now reflected in sections 4.5 and 5.2 of the SmPC. Additionally, it was observed that the pharmacokinetics of ustekinumab from study C0743T25 (a phase 3 study in Korean and Taiwanese subjects) were generally comparable between Asian and non-Asian subjects with psoriasis, with some numerical differences in serum ustekinumab concentrations which might be attributed to cross-study comparisons, inter-subject variability, and most likely, the difference in body weight between the 2 populations. Section 5.2 of the SmPC has been updated to reflect this information.
IG/0090/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/07/2011	n/a		
IB/0014	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	17/05/2011	n/a		

IB/0013/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	31/03/2011	n/a		
IA/0012/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding	15/02/2011	n/a	Annex II and PL	

	manufacturer for batch release)				
IA/0011	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	06/01/2011	n/a		
II/0008/G	This was an application for a group of variations. To add new manufacturing sites for active substance. To change the current approved manufacturing process. To add CBIL as a release and stability testing site of STELARA drug substance and the drug product Vials and Pre-filled Syringes. To change in IPC methods B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method	18/11/2010	20/12/2010	SmPC, Annex II and PL	

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0007/G	This was an application for a group of variations. This application was submitted for a group of variations consisting of two Type II variations. One type II variation is to update sections 4.4 and 4.8 of the SPC with information on hypersensitivity reactions further to the assessment of PSUR 1, and to update the relevant section of the PL and the educational materials accordingly. The other type II variation is to update section 4.4 of the SPC to state the lack of data on secondary transmission of live vaccines and the lack of evidence that Stelara affects allergy immunotherapy. Additionally, the MAH took this opportunity to include administrative changes in Annex IIB. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC -	22/07/2010	26/08/2010	SmPC, Annex II and PL	The MAH conducted a cumulative review of hypersensitivity reactions reported in clinical trials and in the post-marketing setting in which 18 cases were identified (6 from clinical trials and 12 post-marketing). The majority of non-serious cases reported rash or urticaria; three serious post-marketing cases were reported (hypersensitivity, angioedema). The CHMP concluded that a warning about the possibility of delayed hypersensitivity should be added to section 4.4 of the SPC, and that the respective adverse drug reactions should be added to section 4.8. It is in general possible that secondary transmission of live vaccine viruses from individuals vaccinated with such vaccines to contacts of the vaccine recipients occurs. There are no data available on such secondary transmission of infection by live vaccines in patients receiving Stelara. Nevertheless the CHMP accepted the inclusion of such precautionary statement in section 4.4 of the SPC. Finally, there is a theoretical risk that that treatment of patients who have undergone allergy immunotherapy could alter the protection conferred by the allergy immunotherapy based on the mechanism of action of Stelara. Although there is no evidence that Stelara may affect allergy immunotherapy, the CHMP accepted to

	Change(s) with new additional data submitted by the MAH				include such statement in section 4.4 of the SPC.
IB/0010	B.I.b.z - Change in control of the AS - Other variation	24/08/2010	n/a		
IA/0009	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	29/07/2010	n/a		
IG/0007	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	04/06/2010	n/a	Annex II	
II/0006	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 005 to include non-QPPV related changes. Consequently, Annex II has been updated with the new version number of the DDPS. Update of DDPS (Pharmacovigilance)	18/02/2010	15/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 005) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
X/0002	Addition of a new pharmaceutical form Annex I_2.(d) Change or addition of a new pharmaceutical form	17/12/2009	11/03/2010	SmPC, Annex II, Labelling and PL	
II/0005	Extension of shelf life of drug substance intermediates. Change(s) to shelf-life or storage conditions	18/02/2010	01/03/2010		

II/0004	Changes related with the QC testing sites Change(s) to the manufacturing process for the active substance	17/12/2009	07/01/2010		
II/0001	Update of section 5.1 of the SPC with clinical data from the ACCEPT trial and weight-based response scores derived from the PHOENIX 1 and PHOENIX 2 studies. Further minor/administrative updates were applied to sections 2, 4.2, 4.4, 4.8, 5.1, 6.6, 8 and 9 of the SPC. The PL was updated accordingly. Annex II was updated with information regarding educational material and the Marketing Authorisation number for Stelara was included in the Labelling. Finally, the information regarding the local representatives in Germany and Greece was updated and the Instructions for Administration at the end of the PL were revised to improve clarity. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/11/2009	22/12/2009	SmPC, Annex II, Labelling and PL	12-week data efficacy data from the ACCEPT trial, an active comparator study of ustekinumab versus etanercept in patients with moderate to severe plaque psoriasis, was included in section 5.1 of the SPC. Additionally, in order to provide further information regarding the currently recommended posology information based on a 2-tiered approach to dosing by weight, clinical efficacy data from the PHOENIX 1 and PHOENIX 2 studies was included in section 5.1.
IA/0003	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	01/10/2009	n/a		